Waitemata
District Health Board
Te Wai Awhina

Dear Colleague,

Your patient,

is taking clozapine (Clopine®), an antipsychotic that can be effective in patients who have failed to respond to, or are intolerant of, other antipsychotics.

This medication can only be initiated by a psychiatrist or psychiatric registrar under supervision. GP prescribing is only permitted for stable patients in collaboration with the treating psychiatrist. However we recognise that we share this patient's care with you, and that clozapine can have serious side effects, so would appreciate your help. Even if you are not prescribing clozapine you may wish to enter clozapine on the patient's medication list, e.g. in MedTech, so that an alert is added to their record and drug interaction warnings will come up even though you are not the prescribing doctor. If you wish to discuss prescribing clozapine please contact the treating psychiatrist.

About 30 % of patients with schizophrenia have a limited response to other antipsychotics. Clozapine is indicated after trials of two other antipsychotics have been unsuccessful in controlling symptoms or poorly tolerated. The response rate to clozapine is up to 60% by 12 months. However there are various issues to be aware of when a patient is taking clozapine and we have detailed these below.

Problems with clozapine

Haematological

The risk of agranulocytosis (about 0.7% in the first six months), means regular blood monitoring must be carried out for the duration of treatment. Tests are weekly for the first 18 weeks (because the risk is highest in this period), and every four weeks thereafter.

Blood collection, and collation and dissemination of results is coordinated by a system involving pharmacies (both hospital and some community pharmacies), all the pathology laboratories, and mental health teams, and is backed up by a monitored database run by Douglas Pharmaceuticals called ClopineConnect. You can freephone the 24-hour ClopineConnect number (0800 435 811) should you have queries about the database or results for one of your patients. The dispensing pharmacy will not provide clozapine for a patient unless they have a recent normal white blood cell (WBC) and neutrophil result.

If signs of infection occur, or blood tests indicate a significant drop in WBCs, a repeat test - marked urgent - should be carried out. A significant drop would be:

- A WBC count falling below 3.5 (10^9/L) in the first 18 weeks of treatment; or
- A neutrophil count falling below 1.5 (10^9/L); or
- A WBC count falling below 3.0 (10^9/L), or a neutrophil count below 1.0 (10^9/L), after week 18; or
- A single WBC drop of ≥ 3 (10^9/L); or
- A cumulative drop of ≥ 3 (10^9/L) within three weeks.

Any of these events require contact with Mental Health Services as the clozapine may need to be stopped.

Patients on clozapine should be reminded to contact their doctor immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints, such as fever or sore throat, and to other evidence of infection which may be indicative of neutropenia. Patients on clozapine who present to any medical centre with signs or symptoms of infection must have an immediate WBC check, with results sought urgently to rule out agranulocytosis.

Each time the patient has a blood test done it is important to request that a copy be sent to both the dispensing pharmacy, and to ClopineConnect. This ensures that the pharmacist can check the results before any medication is dispensed. The Mental Health Team is responsible for coordinating the blood monitoring and supply of treatment but if you would like to routinely receive a copy of the regular blood results then please let the Mental Health Team know.

Interruption of treatment

Clozapine is a continuing therapy. If a patient stops taking their medication, there is a high risk that their previous mental health symptoms will return. The patient should take the correct dose as soon as the error is recognised, unless more than two days worth of doses have been missed. If you are required to restart it please consult the clozapine data sheet, *Re-starting Therapy* and let the Mental Health Team and Pharmacy know.

Other important adverse effects

Constipation is common (up to 15%), can be severe and requires active management (such as regular osmotic laxatives, e.g. lactulose, and short-term stimulant laxative use, e.g. docusate and senna). In severe cases (especially when other constipating medication such as anticholinergic drugs and opiates have been co-prescribed), toxic megacolon has developed, which in some cases has been fatal. Avoid co-prescribing any other medication that causes constipation.

Hypersalivation is common (up to 30%), unpleasant for the patient and occurs more often at night, but treatment is often successful. In particular, prescribing terazosin (1-2mg at night) may be effective. Benztropine (1-2mg) at night may also be effective but must be used cautiously because it can cause constipation.

Metabolic disturbances including weight gain, lipid abnormalities and diabetes are potential complications and we would appreciate you monitoring these three-monthly after starting and then annually (more frequently if indicated).

Myocarditis and cardiomyopathy can occur rarely (reports range from 1 in 500 to 1 in 10,000). The first month of treatment is the highest risk period for myocarditis, however it may occur very rarely later in treatment and some cases have been fatal. Any signs or symptoms of cardiac adverse effects including unexplained fatigue, fever, chest pain, palpitations, shortness of breath, or other symptoms of heart failure need urgent investigation (e.g. ECG, FBC, troponin, CRP, chest x-ray and possible cardiology referral). If myocarditis is suspected then immediate withdrawal of clozapine is recommended and you should contact the Mental Health Team.

Epileptic seizures are uncommon (around 3%) and usually occur at higher doses. Clozapine does not necessarily need to be stopped as addition of sodium valproate will usually be effective. If seizures occur, you should contact the Mental Health Team.

Nocturnal urinary incontinence may occur (5-10%) but treatment is often successful (desmopressin, oxybutynin and ephedrine may be effective). If this occurs, you should contact the Mental Health Team.

Drug interactions

Any drug with the potential for bone-marrow suppression should not be used with clozapine. The commonest examples are cotrimoxazole and carbamazepine. Some drugs and substances can increase or reduce serum levels of clozapine by inducing or inhibiting liver enzymes responsible for clozapine breakdown - and care needs to be taken if co-prescribing (please consult the clozapine datasheet or speak to the dispensing pharmacy).

Chemicals in cigarette smoke (not the nicotine) can lower serum levels of clozapine so sudden cessation of smoking can cause a large rise in clozapine serum levels with associated toxicity. Conversely the serum level of clozapine can be increased by caffeine intake so sudden cessation of regular caffeine can cause a decrease in clozapine levels and possible return of mental health symptoms.

Please find enclosed:

- A Clopine® datasheet
- A Clozapine 'Quick Reference Sheet' summarising the information in this letter

Thank you. Should you have any questions please contact the treating psychiatrist or a hospital/community pharmacist dispensing clozapine.

Regards

Publication number 0182-01-058 (Review date: September 2012)